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Genotype effects on neurodegeneration and neuroadaptation in monoaminergic neurotransmitter systems

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Abstract

Neuroadaptation and neurodegeneration in central dopaminergic and serotonergic systems are central to vulnerability, process and consequences of addictive behavior. Serotonergic dysfunction has been associated with behavior disinhibition and negative mood states that may predispose to excessive alcohol intake, while alcohol-induced stimulation of dopaminergic neurotransmission may encode the reinforcing properties of alcohol consumption. Chronic alcohol intake induces neuroadaptive reductions in striatal dopamine transporter (DAT) and D2 receptor availability, which were reversible during early abstinence. A polymorphism of the DAT gene (SLC6A3) was associated with the in vivo transporter availability in the putamen of abstinent alcoholics and control subjects. The same genotype was associated with severity of alcohol withdrawal symptoms, hypothetically due to interactions of genotype and alcohol-induced neuroadaptation. Reduction in raphe serotonin transporter (5-HTT) availability was observed in abstinent male alcoholics and it may be the result of neurodegeneration rather than reversible neuroadaptation. Neurotoxic reduction in 5-HTT protein expression seems to be limited to homozygous carriers of a long, more transcriptionally active allele of a promoter repeat polymorphism of the 5-HTT gene (SCL6A4). This genotype was also associated with a low level of acute unpleasant effects of alcohol consumption, a factor predisposing to excessive alcohol intake. The time course of neuroadaptation and recovery of monoaminergic neurotransmission in alcohol intake and withdrawal imply that monoamine transporter genotype could profoundly influence alcohol-induced reinforcement and, perhaps, contribute to neurochemical changes which are long lasting or permanent.

Keywords: Dopamine; Serotonin; Brain reward system; Alcoholism; Neurotoxicity

1. Introduction

Alcohol intake affects a multitude of neurochemical processes, posing challenges to researchers attempting to identify the effects relevant to reinforcement and the long-lasting changes which occur in the brains of alcoholics. Alcohol's effects on monoaminergic neurotransmitter systems are of special interest (Higley et al., 1996; Mash et al., 1996) due to the involvement of dopamine and serotonin in reward and behavioral inhibition, and due to new information on genetic variation of these neurotransmitters. The dopaminergic reward system has long been a focus of addiction research, because different drugs of abuse including alcohol stimulate dopaminergic neurotransmission and thus reinforce drug intake (Wise, 1988; di Chiara and Imperato, 1988; Robinson and Berridge, 1993; Robbins and Everitt, 1996). Conversely, serotonergic stimulation of the behavior inhibition system may inhibit ongoing behavior (Gray, 1982), hypothetically due to the unpleasant feelings of punishment encoded by this neurotransmitter system (Cloninger, 1987a). Dysfunction of this "punishment system" due to a serotonergic deficit may predispose towards disinhibited, impulsive drug intake and anti-social behavior (Linnoila et al., 1983; Cloninger, 1987b). Several studies

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among early-onset alcoholics have observed a dysfunction of central serotonergic neurotransmission as assessed by low concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid (5-HIAA in CSF) (Fils-Aime et al., 1996; Le Marquand et al., 1994a). More recently the mood-enhancing effect of higher serotonin release has been confirmed: increase in synaptic serotonin induced by selective serotonin reuptake inhibitors or "ecstasy" (3,4-methylenedioxymetamphetamine; MDMA) decreases negative mood states (Artigas, 1995; Huether et al., 1997). Negative mood states may be a primary correlate of serotonergic hypofunction, while clinical depression or impulsive aggression may develop under the influence of additional factors including social learning or isolation stress (Raleigh and McGuire, 1984, 1991; Knutson et al., 1998).

Alcohol and neurotransmitter functions may interact at least at three levels: genotype, neuroadaptation and neurodegeneration (Halliday et al., 1993; Pato et al., 1993; Koob and LeMoal, 1997; Nestler and Aghajanian, 1997). Studies on these processes in humans and non-human primates are warranted because of important anatomical and functional differences in monoaminergic neurotransmission between rodents and primates (Berger et al., 1991; Lynd-Balta and Haber, 1994a, 1994b) as well as genetic differences which may be specific to the human. The evidence for neuroadaptation and neurodegeneration will be reviewed separately for dopaminergic and serotonergic neurotransmission, followed by a short discussion of general implications.

2. Chronic alcohol effects on central dopaminergic neurotransmission

Alcohol intake stimulates the firing rate of dopaminergic neurons that project to the ventral and dorsal striatum (Mereu et al., 1984; Imperato and di Chiara, 1986). In several studies on rodents, chronic alcohol intake was associated with a counteradaptive down-regulation of post-synaptic striatal dopamine D2 receptors, which recovered within the first week of abstinence (Pellegrino and Druse, 1992; Rommelspacher et al., 1992). In humans, a reduction in striatal dopamine D2 receptor availability was observed in positron-emission-tomography (PET) studies (Hietala et al., 1994; Volkow et al., 1996). A reduction in the sensitivity of central dopamine D2 receptors was also found in challenge studies with the dopamine agonist apomorphine (Balldin et al., 1992; Heinz et al., 1995a). Further studies in alcoholics confirmed that similar to animal studies, the reduction of central D2 receptor sensitivity was not permanent and it returned towards control levels within one week after detoxification. A prolonged recovery of central D2 receptor sensitivity was predictive of subsequent poor treatment outcome (Heinz et al., 1996a), and in some patients with early relapses, dopamine D2 receptor sensitivity did not reach control levels even during a prolonged observation period of three months after detoxification (Fig. 1; Dettling et al., 1995).

As patients with prolonged recovery of central D2 receptors and poor treatment outcome did not differ from treatment responders in the amount of lifetime alcohol consumption or other clinical variables (Dettling et al., 1995; Heinz et al., 1995a), it was suggested that the genetic constitution of the dopamine D2 receptor may mediate prolonged recovery from chronic alcohol intoxication. Studies on D2 genotype versus D2 receptor density which do not take into account prior alcohol exposure and duration of abstinence, are difficult to interpret (Noble et al., 1991). While an exon 8 polymorphism of the dopamine D2 receptor gene (DRD2) was found to interact with central dopaminergic sensitivity during chronic alcohol intoxication (Finckh et al., 1997), no such interactions with either the DRD2 exon 8 or the TaqIA polymorphism were found during early abstinence (Heinz et al., 1996b; Finckh et al., 1997). Studies of Goldman et al. (1997, 1998) did not support the hypothesis that reduced dopamine D2 receptor sensitivity in abstinent alcoholics is genetically determined. They found no association between alcoholism and a functionally relevant polymorphic variant of the D2 receptor protein, the amino acid substitution Ser311 → Cys (Cravchik et al., 1996). A D2 promoter polymorphism which affects the transcription of this gene (Ishiguro et al., 1998) would be of particular interest to evaluate. Meanwhile, several lines of evidence suggested that post-synaptic D2 receptor sensitivity may remain reduced during abstinence because pre-synaptic dopamine release is sensitized even in the absence of chronic alcohol intake. How could that be the case?

3. Conditioned dopamine release in abstinent alcoholics

During detoxification, ethanol-induced dopamine release terminates and synaptic dopamine concentrations decrease. These events occur during the first 24 h of abstinence (Rossetti et al., 1992). However, phasic dopamine release may be stimulated during abstinence by conditioned stimuli ("cues") previously been associated with alcohol reward (Schultz et al., 1993, 1997; Robinson and Berridge, 1993). The stimulus-dependent dopamine release attributes incentive salience to the conditioned stimulus, and may subjectively be experienced as craving for the drug reward which was originally associated with the conditioned cue (Berridge and Robinson, 1998). Stimulus-depen-

dent, sensitized dopamine release may be both frequent and substantial: studies of pre-synaptic striatal dopamine synthesis with DOPA-PET and of peripheral and central concentrations of dopamine and its major metabolite, homovanillic acid (HVA), indicate that dopamine turnover is increased among abstinent alcoholics (George et al., 1992, 1999; Heinz et al., 1995b; Tiihonen et al., 1998). Further, in three of these studies, the indices of increased dopamine turnover were associated with poor treatment outcome (George et al., 1992, 1999; Heinz et al., 1996b). Post-synaptic D2 receptor down-regulation in the striatum may thus compensate for the sensitized conditioned pre-synaptic dopamine release (Fig. 1).

4. Alcohol effects on dopamine transporter availability during early abstinence

The effects of increased pre-synaptic dopamine release may be potentiated by reduced dopamine clearance from the synaptic cleft. Dopamine transporters play a major role in the regulation of synaptic dopamine concentrations (Giros et al., 1996; Heinz et al., 1999). The dopamine transporter could respond to chronic alcohol administration. In fact, Tiihonen et al. (1995) observed reduced dopamine transporter availability measured with single-photon-emission-tomography (SPECT) in the striatum of alcoholics with late disease onset. However, two other studies failed to confirm a reduction in dopamine transporters in alcoholics (Volkow et al., 1996; Heinz et al., 1998a). A study of Laine et al. (1999) showed that the time course of recovery during detoxification may explain the heterogeneous study results: striatal dopamine transporter availability was reduced in alcoholics who had been detoxified for four days, however, it had increased towards a normal range when the subjects were tested again after four weeks of abstinence. In the study of Tiihonen et al. (1995), alcoholics had not been selected for duration of abstinence, and data collection in subjects scanned early after detoxification may have influenced the study results.

5. Genotype effects on dopamine transporter availability

Another factor that may affect in vivo dopamine transporter (DAT) availability is the genetic constitution of the DAT protein or genetic differences in transcription of this gene or the function of its mRNA. A polymorphism of the 3′ untranslated region of the DAT gene (SLC6A3; Vandenbergh et al., 1992; Sano et al., 1993) has been associated with the severity of withdrawal symptoms among alcoholics (Sander et al., 1997; Schmidt et al., 1998). Further, Gelernter et al. (1994) observed a significant association of this polymorphism with paranoia induced by cocaine, a potent DAT blocker, and Sabol et al (1999) recently reported association of this polymorphism with the ease of smoking cessation. Because each of these clinical associations could conceivably be explained by genetically determined variations in synaptic dopamine, a brain imaging study assessed the relationship of this polymorphism to variations in the availability of the DAT protein (Heinz et al., 2000a). The variable number of tandem repeat (VNTR) polymorphism in the 3′ region of SLC6A3 was genotyped and the availability of striatal DAT protein was measured in abstinent alcoholics and control subjects. Single photon emission computed tomography (SPECT) with the radioligand [I-123]-2β-carbomethoxy-3β-(4-iodophenyl)tropane ([I-123] β-CIT) was used to determine the effective binding potential, a quantitative measure of DAT availability (Laruelle et al., 1993, 1994).

Consistent with earlier studies, striatal dopamine transporter availability was not reduced among alcoholics after four weeks of abstinence (Volkow et al.,

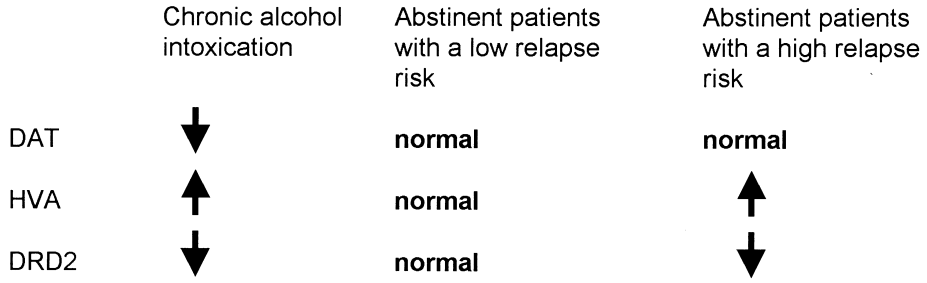

Fig. 1. Pre- and post-synaptic dopamine release, turnover and reuptake in alcohol-preferring primates during chronic alcohol intake and in alcoholics during chronic alcohol intoxication and abstinence. Alcohol stimulates the firing rate of dopaminergic neurons and chronic alcohol consumption seems to induce a down-regulation of dopamine transporters (Mash et al., 1996; Laine et al., 1999) and central dopamine D2 receptors (DRD2) (Heinz et al., 1996a, 1996b; Volkow et al., 1996). During early abstinence, alcoholics with a good treatment outcome showed rapid recovery of dopaminergic neurotransmission while alcoholics with poor treatment outcome displayed a high dopamine turnover rate and a reduced sensitivity of central dopamine D2 receptors (George et al., 1992, 1999; Dettling et al., 1995; Heinz et al., 1995, 1996a), hypothetically due to a sensitization of dopaminergic neurotransmission (Robinson and Berridge, 1993).

1996; Laine et al., 1999). Nor was alcoholism per se associated with DAT genotype. However, DAT genotype was associated with transporter availability in the putamen: individuals with the 9-repeat/10-repeat genotype had a mean 22% reduction of DAT protein availability in putamen compared with 10-repeat homozygous individuals (Heinz et al., 2000a). This finding suggest that the VNTR polymorphism of the DAT gene affects DAT protein levels. The differences in DAT availability may be clinically important during early withdrawal, when rapid changes of dopamine release occur (Rossetti et al., 1992; Heinz et al., 1995a, 1996a). This observation may explain the association between this DAT polymorphism and severity of alcohol withdrawal symptoms and other clinical phenomena (Gelernter et al., 1994; Sander et al., 1997; Schmidt et al., 1998; Sabol et al., 1999).

6. Dopamine transporter changes in alcoholism: neurodegeneration or neuroadaptation?

During early abstinence, both alcohol and genotype effects seem to influence DAT availability. It is not known why DAT availability is reduced within the first days of abstinence (Laine et al., 1999). The rapid recovery of striatal dopamine transporters observed by Mash et al. (1996) and Laine et al. (1999) mirrors the changes in other areas of dopaminergic neurotransmission such as dopamine receptor sensitivity (Heinz et al., 1995b). The normal DAT availability observed among alcoholics after a few weeks of abstinence (Volkow et al., 1996; Heinz et al., 1998a; Laine et al., 1999) argues against a previous loss of dopamine transporters due to neurodegeneration, which may probably not be compensated within such a short time. Eshleman et al. (1993) suggested that alcohol-induced dopamine release may be in part mediated by dopamine transporters in a functional reversal of their normal role. If this is the case, a down-regulation of pre-synaptic dopamine transporters may help to counteract alcohol effects on the dopaminergic system. It would thus represent a neuroadaptive process similar to the down-regulation of post-synaptic D2 receptors, which may explain the comparable time course of recovery during early abstinence (Fig. 1; Heinz et al., 1995b; Mash et al., 1996; Laine et al., 1999). Further studies will have to be done to characterize the role of the dopamine transporter in chronic alcohol intake.

7. Alcohol and genotype effects on raphe nuclei serotonin transporters

In humans and non-human primates, serotonin transporter availability can be measured with SPECT and the radioligand β-CIT in the dorsal brainstem (raphe nuclei) area, the site of origin of subcortical and cortical serotonin projections (Laruelle et al., 1993; Heinz et al., 1998a, 1998b). In the raphe area, β-CIT is exclusively displaced by selective serotonin reuptake inhibitors but not substances such as GBR, which selectively bind to dopamine transporters (Laruelle et al., 1993). Among male alcoholics, a reduction of raphe serotonin transporters has been observed after four weeks of abstinence (Heinz et al., 1998a). Loss of serotonin transporters in male alcoholics thus seems to be more profound or persistent than reductions in striatal dopamine transporters, which usually returned to normal levels at this time of abstinence (Heinz et al., 1998a; Laine et al., 1999). In accordance with this observation, Halliday et al. (1993) observed a significant loss of brainstem serotonergic cells in alcoholics. As a substantial number of neurons that originate in the raphe area innervate other raphe nuclei (Baumgarten and Grozdanovic, 1997), a loss of serotonergic neurons would also affect the density of presynaptic serotonin transporters in this brain area. The reduction in serotonin transporters among male alcoholics was correlated with the amount of lifetime alcohol intake and may thus represent a neurotoxic effect of chronic alcohol consumption on brainstem serotonin neurons and transporters (Heinz et al., 1998a).

The reduction of raphe serotonin transporters was, however, not observed among all male alcoholics but only in a specific genetic subgroup, namely homozygote carriers of the long (“*l*”) allele of the promoter for the serotonin transporter gene (“*ll*-homozygotes”) (Heinz et al., 2000b). It has been suggested by Lesch et al. (1996) that this genotype is associated with an increased serotonin transporter density and functional capacity among healthy control subjects, and a similar increase in serotonin transporter availability was observed in this genotype among male healthy control subjects in vitro (Little et al., 1998) and in vivo (Fig. 2; Heinz et al., 2000b). In a prospective study of young men over 15 years, this genotype was associated with low acute unpleasant effects of alcohol intake before chronic alcohol intake was started and with an increased risk to develop alcoholism (Schuckit et al., 1999). Interestingly, an increased availability of brainstem serotonin transporters was also associated with reduced CSF 5-HIAA concentrations, low acute alcohol effects and a disposition towards excessive alcohol consumption among male non-human primates (Heinz et al., 1998b). After chronic alcohol intake, this same genotype may render subjects vulnerable to the toxic effects of chronic alcohol intake and thus result in a pronounced loss of raphe serotonin transporters (Fig. 2; Heinz et al., 2000b). An alternative interpretation is based on the fact that the radioligand β-CIT

competes with endogenous serotonin for binding at the serotonin reuptake sites (Jones et al., 1998). Therefore, the in vivo decrease in serotonin transporter availability among male abstinent *ll*-homozygote alcoholics may be due to increased synaptic serotonin concentrations and not to a real loss of serotonin transporters.

This interpretation, however, is not easily reconciled with the observation of reduced brainstem serotonergic neurons among alcoholics (Halliday et al., 1993). This latter observation may indicate that the in vivo observation of reduced radioligand binding to serotonin transporters represents a loss of reuptake sites in the raphe area due to alcohol-induced neurodegeneration.

8. Summary and general implications

A few conclusions can be drawn from this review of genotype effects on monoaminergic neuroadaptation and neurodegeneration in alcoholism. Firstly, it is of primary importance to monitor the time course of changes in dopaminergic and monoaminergic neurotransmission during chronic alcohol intake and abstinence. Several studies indicated that alcohol consumption stimulates dopamine and serotonin release (Imperato and di Chiara, 1986; Le Marquand et al., 1994a; 1994b) and induces post- and also potentially pre-synaptic neuroadaptation (Mash et al., 1996; Heinz et al., 1995a; Laine et al., 1999). These neuroadaptive changes seem to recover during early abstinence with a wide inter-individual variation, which may be predictive of the relapse risk of alcoholics (Heinz et al., 1996a). Measurements of monoaminergic neurotransmission that include only one time point thus run the risk of mistaking a state of neuroadaptation or recovery for persistent neurodegeneration. Secondly, it is important to assess several factors of monoaminergic neurotransmission simultaneously. Increased stimulus-dependent dopamine release may be associated with an adaptive down-regulation of post-synaptic dopamine D2 receptors (Heinz et al., 1999), and a reduction in dopamine or serotonin reuptake sites may be correlated with increased synaptic neurotransmitter concentrations (Giros et al., 1996; Heinz et al., 1998b, 1999). An observed reduction in striatal dopamine transporters during chronic alcohol intake can, therefore, not be interpreted as an indication of reduced dopaminergic neurotransmission, but may even be associated with indicators of increased dopamine turnover (Mash et al., 1996). Thirdly, genotype effects have been observed that may modify neuroadaptation and neurodegeneration of monoamine transporters. The genetic constitution of the DAT gene was

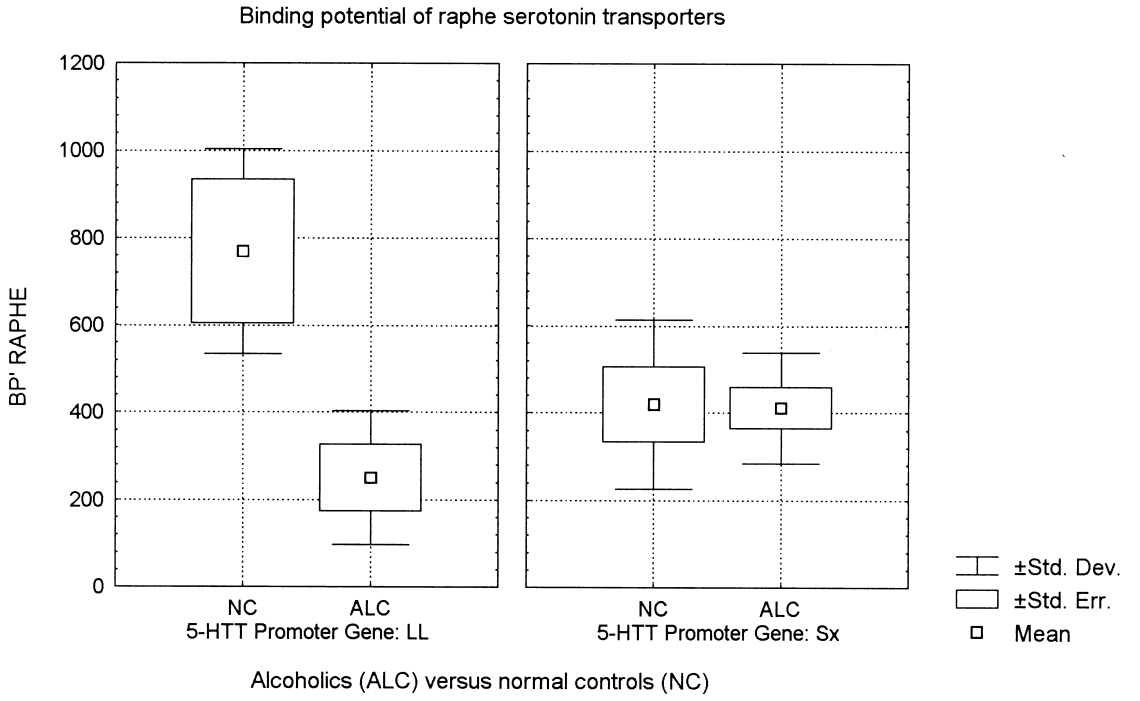

Fig. 2. Effective binding potential (BP′) of the radioligand β-CIT to serotonin transporters in the raphe area of homozygous carriers of the long allele (*ll*-homozygotes: *LL*; **left**) versus carriers of the short allele (*s*-carriers:, *Sx*; **right**) of the promoter for the serotonin transporter (5-HTT) gene in normal controls (NC) and alcoholics (ALC). In accordance with in vitro data (Lesch et al., 1996), *ll*-homozygote control subjects displayed a significant increase in the availability of raphe 5-HTT as compared with *s*-carriers. Among alcoholics, only *ll*-homozygotes showed significantly reduced availability of raphe serotonin transporters, potentially due to the effects of long-term alcohol intoxication in this genotype.

associated with in vivo transporter availability in the putamen (Heinz et al., 2000a) and it may interact with the severity of alcohol withdrawal symptoms during the first days of abstinence (Sander et al., 1997; Schmidt et al., 1998), when dopamine transporters are still recovering from the effects of chronic alcohol intake (Mash et al. 1996; Laine et al., 1999). A longer-lasting, potentially permanent reduction in serotonin transporters was found in a genetically defined subgroup of male alcoholics, who were homozygous carriers of a long, transcriptionally more active allele of the promoter for the serotonin transporter gene (Heinz et al., 2000b). Subjects with this genotype were predisposed to excessive alcohol intake (Schuckit et al., 1999) and may be specifically vulnerable to chronic alcohol intoxication (Heinz et al., 2000b). The reason for this vulnerability is not known and may include toxic effects on raphe neurons, effects of alcohol withdrawal or stress-induced cortisol release (Slotkin et al., 1997). Further studies will be necessary to characterize better the genotype-environmental interactions that modify monoamine neurotransmitter release and reuptake in alcoholism so that potentially reversible neuroadaptations can be distinguished from neurodegeneration.

References

Artigas, F., 1995. Pindolol, 5-hydroxytryptamine, and antidepressant augmentation. Archives of General Psychiatry 52, 969–971.

Balldin, J.I., Berggren, U.C., Lindstedt, G., 1992. Neuroendocrine evidence for reduced dopamine receptor sensitivity in alcoholism. Alcoholism: Clinical and Experimental Research 16, 71–74.

Baumgarten, H.G., Grozdanovic, Z., 1997. Anatomy of central serotoninergic projection systems. In: Baumgarten, H.G., Göthert, M. (Eds.), Handbook of Experimental Pharmacology: Serotoninergic Neurons and 5-HT Receptors in the CNS, vol. 129. Springer, Berlin, Heidelberg, pp. 41–89.

Berger, B., Gaspar, P., Verney, C., 1991. Dopaminergic innervation of the cerebral cortex: unexpected differences between rodents and primates. Trends in Neuroscience 14, 21–27.

Berridge, K.C., Robinson, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Research Reviews 28, 309–369.

Cloninger, C.R., 1987a. A systematic method for clinical description and classification of personality variants: a proposal. Archives of General Psychiatry 44, 573–588.

Cloninger, C.R., 1987b. Neurogenetic adaptive mechanisms in alcoholism. Science 236, 410–416.

Cravchik, A., Sibley, D.R., Gejman, P.V., 1996. Functional analysis of the human D2 receptor missense variants. Journal of Biology and Chemistry 271, 26013–26017.

Dettling, M., Heinz, A., Dufeu, P., Rommelspacher, H., Gräf, K.J., Schmidt, L.G., 1995. Dopaminergic responsivity in alcoholism: trait-, state- or residual marker? American Journal of Psychiatry 152, 1317–1321.

di Chiara, G., Imperato, A., 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proceedings of the National Academy of Science USA 85, 5274–5278.

Eshleman, A.J., Henningsen, R.A., Neve, K.A., Janowsky, A., 1993. Release of dopamine via the human transporter. Molecular Pharmacology 45, 312–316.

Fils-Aime, M.L., Eckhardt, M.J., George, D.T., Brown, G.L., Mefford, I., Linnoila, M., 1996. Early-onset alcoholics have lower cerebrospinal fluid 5-hydroxyindoleacetic acid levels than late-onset alcoholics. Archives of General Psychiatry 53, 211–216.

Finckh, U., Rommelspacher, H., Kuhn, S., Dufeu, P., Otto, G., Heinz, A., Dettling, M., Giraldo-Velasquez, M., Pelz, J., Gräf, K.J., Harms, H., Sander, T., Schmidt, L.G., Rolfs, A., 1997. Influence of the dopamine D2 receptor (DRD2) genotype on neuroadaptive effects of alcohol and the clinical outcome of alcoholism. Pharmacogenetics 7, 271–281.

Gelernter, J., Kranzler, H.R., Satel, S.L., Rao, P.A., 1994. Genetic association between dopamine transporter protein alleles and cocaine-induced paranoia. Neuropsychopharmacology 11, 195–200.

George, D.T., Lindquist, T., Rawlings, R.R., Eckhardt, M.J., Moss, H., Mathis, C., Martin, P.R., Linnoila, M., 1992. Pharmacologic maintenance of abstinence in patients with alcoholism. Clinical Pharmacology and Therapeutics 52, 553–560.

George, D.T., Rawlings, R., Eckhardt, M.J., Phillips, M.J., Shoaf, S., Linnoila, M., 1999. Buspirone does not promote treatment compliance for patients with alcoholism: age of onset, CSF 5-HIAA and HVA predictors of noncompliance. Alcoholism: Clinical and Experimental Research 23, 272–278.

Giros, B., Jaber, M., Jones, S.R., Wightman, R.M., Caron, M.G., 1996. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. Nature 379, 606–612.

Goldman, D., Urbanek, M., Guenther, D., Robin, R., Long, J.C., 1997. Linkage and association of a functional DRD2 variant [Ser311Cys] and DRD2 markers to alcoholism, substance abuse and schizophrenia in Southwestern American Indians. American Journal of Genetics 74, 386–394.

Goldman, D., Urbanek, M., Guenther, D., Robin, R., Long, J.C., 1998. A functionally deficient DRD2 variant [Ser311Cys] is not linked to alcoholism and substance abuse. Alcohol 16, 47–52.

Gray, J.A., 1982. The neuropsychology of anxiety. In: An Inquiry into the Function of the Septo-Hippocampal System. Oxford University Press, New York.

Halliday, G., Ellis, J., Heard, R., Caine, D., Harper, C., 1993. Brainstem serotonergic neurons in chronic alcoholics with and without Korsakoff's Psychosis. Journal of Neuropathology and Experimental Neurology 52, 567–579.

Heinz, A., Dettling, M., Kuhn, S., Gräf, K.J., Kürten, I., Rommelspacher, H., Schmidt, L.G., 1995a. Blunted growth hormone response is associated with early relapse in alcohol-dependent patients. Alcoholism: Clinical and Experimental Research 19, 62–65.

Heinz, A., Lichtenberg-Kraag, B., Sällström Baum, S., Gräf, K., Krüger, F., Dettling, M., Rommelspacher, H., 1995b. Evidence for prolonged recovery of dopaminergic transmission in alcoholics with poor treatment outcome. Journal of Neural Transmission 2, 149–158.

Heinz, A., Dufeu, P., Kuhn, S., Dettling, M., Gräf, K.J., Kürten, I., Rommelspacher, H., Schmidt, L.G., 1996a. Psychopathological and behavioral correlates of dopaminergic sensitivity in alcohol-dependent patients. Archives of General Psychiatry 53, 1123–1128.

Heinz, A., Sander, T., Harms, H., Finckh, U., Kuhn, S., Dufeu, P., Dettling, M., Gräf, K., Rolfs, A., Rommelspacher, H., Schmidt, L.G., 1996b. Lack of allelic association of dopamine D1 and D2 (TaqA1) receptor gene polymorphism with reduced dopaminergic sensitivity in alcoholism. Alcoholism: Clinical and Experimental Research 20, 1109–1113.

Heinz, A., Ragan, P., Jones, D.W., Hommer, D., Williams, W.,

Knable, M.B., Gorey, J., Doty, L., Geyer, C., Lee, K.S., Coppola, R., Weinberger, D.R., Linnoila, M., 1998a. Reduced serotonin transporters in alcoholism. American Journal of Psychiatry 155, 1544–1549.

Heinz, A., Higley, J.D., Jones, D.W., Gorey, J.G., Saunders, R., Zajicek, K., Suomi, S.S., Knable, M.B., Weinberger, D.R., Linnoila, M., 1998b. In vivo observation of an association between serotonin transporters and sensitivity to alcohol intoxication. American Journal of Psychiatry 155, 1023–1028.

Heinz, A., Saunders, R.C., Kolachana, B.S., Bertolino, A., Jones, D.W., Gorey, J.G., Bachevalier, J., Lee, K.S., Knable, M.B., Saunders, R.C., Weinberger, D.R., 1999. Disinhibition of subcortical dopaminergic neurotransmission in rhesus monkeys with neonatal mesial temporal lesions. Synapse 39, 71–79.

Heinz, A., Goldman, D., Jones, D.W., Palmour, R., Hommer, D., Gorey, J.G., Lee, K.S., Linnoila, M., Weinberger, D.R., 2000a. Genetic effects on striatal dopamine transporter availability. Neuropsychopharmacology 22, 132–139.

Heinz, A., Jones, D.W., Mazzanti, C., Goldman, D., Ragan, P., Hommer, D., Linnoila, M., Weinberger, D.R., 2000b. Serotonin transporter genotype interacts with in vivo protein expression and chronic alcohol intake. Biological Psychiatry, 47, 643–649.

Hietala, J., West, C., Sylvälahti, E., Nygren, K., Lehikoinen, P., Sonninen, P., Ruotsalainen, U., 1994. Striatal dopamine receptor binding characteristics in vivo in patients with alcohol dependence. Psychopharmacology 116, 285–290.

Higley, J.D., Suomi, S.S., Linnoila, M., 1996. A non-human primate model of type II excessive alcohol consumption. Part 1 & 2. Alcoholism: Clinical and Experimental Research 20, 629–651.

Huether, G., Zhou, D., Rüther, E., 1997. Causes and consequences of the loss of serotonergic presynapses elicited by the consumption of 3,4-methylenedioxymetamphetamine (MDMA, "ecstasy") and ist congeners. Journal of Neural Transmission 104, 771–794.

Imperato, A., di Chiara, G., 1986. Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. Journal of Pharmacology and Experimental Therapeutics 239, 219–228.

Ishiguro, H., Arinami, T., Saito, T., Akazawa, S., Enomoto, M., Mitushio, H., Fujishiro, H., Tada, K., Akimoto, Y., Mifune, H., Shioduka, S., Hamaguchi, H., Tour, M., Shibuya, H., 1998. Association study between the −141C Ins/Del and TaqIA polymorphism of the dopamine D2 receptor gene and alcoholism. Alcoholism: Clinical and Experimental Research 22, 845–848.

Jones, D.W., Gorey, J.G., Zajicek, K., Das, S., Urbina, R.A., Lee, K.S., Heinz, A., Knable, M.B., Higley, D.R., Weinberger, D., Linnoila, M., 1998. Depletion–restoration studies reveal the impact of endogenous dopamine and serotonin on [I-123]β-CIT SPECT imaging in primate brain. Journal of Nuclear Medicine 39 (Suppl) (42 pp).

Knutson, B., Wolkowitz, O.M., Cloe, S.W., Moore, E.A., Johnson, R.C., Terpstra, J., Turner, R.A., Reus, V.I., 1998. Selective alteration of personality and social behavior by serotonergic intervention. American Journal of Psychiatry 155, 373–379.

Koob, G.F., Le Moal, M., 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278, 52–58.

Laine, T.P., Ahonen, A., Torniainen, P., Heikkilä, J., Pyhtinen, J., Räsänen, P., Niemelä, O., Hillborn, M., 1999. Dopamine transporters increase in human brain after alcohol withdrawal. Molecular Psychiatry 4, 189–191.

Laruelle, M., Baldwin, R.M., Malison, R.T., Zea-Ponce, Y., Zoghbi, S.S., Al-Tikriti, M.S., Sybirska, E.H., Zimmermann, R.C., Wisniewski, G., Neumeyer, J.L., Milius, R.A., Wang, S., Smith, E.O., Roth, R.H., Charney, D.S., Hoffer, P.B., Innis, R.B., 1993. SPECT imaging of dopamine and serotonin transporters with [123-I]β-CIT: pharmacological characterization of brain uptake in non-human primates. Synapse 13, 295–309.

Laruelle, M., Wallace, A., Seibyl, J.P., Baldwin, R.M., Zea-Ponce, Y., Zoghbi, S.S., Neumeyer, J.L., Charney, D.S., Hoffer, P.B., Innis, R.B., 1994. Graphical, kinetic, and equilibrium analyses of in vivo [123-I]β-CIT binding to dopamine transporters in healthy human subjects. Journal of Cerebral Blood Flow and Metabolism 14, 982–994.

Le Marquand, D., Phil, R.O., Benkelfat, C., 1994a. Serotonin and alcohol intake, abuse, and dependence: clinical evidence. Biological Psychiatry 36, 326–337.

Le Marquand, D., Pihl, R.O., Benkelfat, C., 1994b. Serotonin and alcohol intake, abuse, and dependence: findings of animal studies. Biological Psychiatry 36, 395–421.

Lesch, K.P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Muller, C.R., Hamer, D.H., Murphy, D.L., 1996. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274, 1527–1531.

Linnoila, M., Virkunnen, M., Scheinin, M., Nuutila, A., Rimon, R., Goodwin, F.K., 1983. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sciences 33, 2609–2614.

Little, K.Y., McLaughlin, D.P., Zhang, L., Livermore, C.S., McFinton, P.R., DelProposto, Z.S., Hill, E., Cassin, B.J., Watson, S.J., Cook, E.H., 1998. Cocaine, ethanol, and genotype effects on human midbrain serotonin transporter binding sites and mRNA levels. American Journal of Psychiatry 155, 207–213.

Lynd-Balta, E., Haber, S.N., 1994a. The organization of midbrain projections to the ventral striatum in the primate. Neuroscience 53, 609–623.

Lynd-Balta, E., Haber, S.N., 1994b. The organization of midbrain projections to the ventral striatum in the primate: sensorimotor-related striatum versus ventral striatum. Neuroscience 53, 625–640.

Mash, D.C., Staley, J.K., Doepel, F.M., Yound, S.N., Ervin, F.R., Palmour, R.M., 1996. Altered dopamine transporter densities in alcohol-preferring vervet monkeys. NeuroReport 7, 457–462.

Mereu, G., Fadda, F., Gessa, G.L., 1984. Ethanol stimulates the firing rate of nigral neurons in unanesthetized rats. Brain Res. 292, 63–69.

Nestler, E.J., Aghajanian, G.K., 1997. Molecular and cellular basis of addiction. Science 278, 58–63.

Noble, E.P., Blum, K., Ritchie, T., Montgomery, A., Sheridan, P.J., 1991. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. Archives of General Psychiatry 48, 648–654.

Pato, C.N., Macchiardi, F., Pato, M.T., Verga, M., Kennedy, J.L., 1993. Review of the putative association of the D2 dopamine receptor and alcoholism: a meta-analysis. American Journal of Genetics (Neuropsychiatric Genetics) 48, 78–82.

Pellegrino, S.M., Druse, M.J., 1992. The effects of chronic ethanol consumption on the mesolimbic and nigrostriatal dopamine system. Alcoholism: Clinical and Experimental Research 16, 275–280.

Raleigh, M.J., McGuire, M.T., 1984. Social and environmental influences on blood serotonin concentrations in monkeys. Archives of General Psychiatry 41, 405–410.

Raleigh, M.J., McGuire, M.T., 1991. Bidirectional relationship between tryptophan and social behavior in vervet monkeys. In: Schwarcz, R., Young, S.N., Brown, R.R. (Eds.), Kynurenine and Serotonin Pathways. Progress in Tryptophan Research. Plenum Press, New York, London, pp. 289–298.

Robbins, T.W., Everitt, B.J., 1996. Neurobehavioral mechanisms of reward and motivation. Current Opinions in Neurobiology 6, 228–236.

Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Research Reviews 18, 247–291.

Rommelspacher, H., Raeder, C., Kaulen, P., Brüning, G., 1992.

Adaptive changes of dopamine-D2 receptors in rat brain following ethanol withdrawal: a quantitative autoradiographic investigation. Alcohol 9, 1–8.

Rossetti, Z.L., Melis, F., Carboni, S., Diana, M., Gessa, G.L., 1992. Alcohol withdrawal in rats is associated with a marked fall in extraneural dopamine. Alcoholism: Clinical and Experimental Research 16, 529–532.

Sabol, S.Z., Nelson, M.L., Fisher, C., Gunzerath, L., Brody, C.L., Hu, S., Sirota, L.A., Marcus, S.E., Greenberg, B.D., Lucas, F.R.IV., Benjamin, J., Murphy, D.L., Hamer, D.H., 1999. A genetic association for cigarette smoking behavior. Health Psychology 18, 7–13.

Sander, T., Harms, H., Podschus, J., Finckh, U., Nickel, B., Rolfs, A., Rommelspacher, H., Schmidt, L.G., 1997. Allelic association of a dopamine transporter gene polymorphism in alcohol dependence with withdrawal seizures or delirium. Biological Psychiatry 41, 299–304.

Sano, A., Kondoh, K., Katimoto, Y., Kondo, I., 1993. A 40-nucleotide repeat polymorphism in the human dopamine transporter gene. Human Genetics 91, 405–406.

Slotkin, T.A., McCook, E.C., Ritchie, J.C., Caroll, B.J., Seidler, F.J., 1997. Serotonin transporter expression in rat brain regions and blood platelets: aging and glucocorticoid effects. Biological Psychiatry 41, 172–183.

Schmidt, L.G., Harms, H., Kuhn, S., Rommelspacher, H., Sander, T., 1998. Modification of alcohol withdrawal by the A9 allele of the dopamine transporter gene. American Journal of Psychiatry 155, 474–478.

Schuckit, M.A., Mazzanti, C., Smith, T.L., Ahmed, U., Radel, M., Iwata, N., Goldman, D., 1999. Selective genotyping for the role of 5-HT_{2A}, 5-HT_{2C}, and $GABA_{\alpha 6}$ receptors and the serotonin transporter in the level of response to alcohol: a pilot study. Biological Psychiatry 45, 647–651.

Schultz, W., Apicella, P., Ljungberg, T., 1993. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. Journal of Neuroscience 13, 900–913.

Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1599.

Tiihonen, J., Kuikka, J., Bergström, K., Hakola, P., Karhu, J., Ryynänen, O.P., Föhr, J., 1995. Altered striatal dopamine reuptake stites in habitually violent and non-violent alcoholics. Nature Medicine 1, 654–657.

Tiihonen, J., Vilkman, H., Räsönen, P., Ryynänen, O.P., Hakko, H., Bergman, J., Hämäläainen, T., Laakso, A., Haaparanta-Solin, M., Solin, O., Kuoppamäki, M., Sylvalathi, E., Hietala, J., 1998. Striatal presynaptic dopamine function in type 1 alcoholics measured with positron emission tomography. Molecular Psychiatry 4, 156–161.

Vandenbergh, D.J., Persico, A.M., Hawkins, A.L., Griffin, C.A., Li, X., Jabs, E.W., Uhl, G.R., 1992. Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. Genomics 14, 1104–1106.

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Hitzemann, R., Ding, Y.S., Pappas, N., Shea, C., Piscani, K., 1996. Decreases in dopamine receptors but not in dopamine transporters in alcoholics. Alcoholism: Clinical and Experimental Research 20, 1594–1598.

Wise, R.A., 1988. The neurobiology of craving: implications for the understanding of addiction. Journal of Abnormal Psychology 97, 118–132.